Remarks

The Office Action mailed December 2, 2005, has been received and reviewed. Claims 1, 2, 8, 9, 12, 14, 15, 18, 26, 27, and 31-35 having been amended, and claims 20 and 21 having previously been cancelled, without prejudice, the pending claims are claims 1-19 and 22-35. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim 1 has been amended to include the recitations of dependent claim 8, as presented in the previous Amendment and Response (filed September 29, 2005). Dependent claim 8, however, has not been cancelled; it has instead been amended to correspond to dependent claim 2, as originally filed.

Dependent claim 2 has been rewritten as an independent claim and includes the recitations of the base claim from which it previously depended (claim 1, as presented in the previous Amendment and Response (filed September 29, 2005)).

Dependent claim 15 has been rewritten as an independent claim and includes the recitations of the base claim from which it previously depended (claim 14, as originally filed.

Claims 9, 12, 14, 26, 31, 33, and 34 have been amended to include the recitations of claim 8, as presented in the previous Amendment and Response (filed September 29, 2005).

Claims 12, 32, and 33 have been amended for clarity, following the Examiner's suggestions.

Claim 26 has been amended to correct the format of the method claim; claim 27 has been amended to correct an inadvertent typographical error; and claim 35 has been amended to correct inadvertent grammatical errors.

Applicants respectfully submit that no new matter is added and no new issues for search or examination are raised by the amendment of claims 1, 2, 8, 9, 12, 14, 15, 18, 26, 27, and 31-35. The entry and allowance of amended claims 1, 2, 8, 9, 12, 14, 15, 18, 26, 27, and 31-35 is respectfully requested.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 12, 32-33, and 35 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Reconsideration and withdrawal of this rejection is respectfully requested.

Specifically, the Examiner asserted that the recitation "the treated specimen" in claim 12 lacks proper antecedent basis. As recommended by the Examiner, claim 12 has been amended to recite "the exposed specimen." Applicants submit that this rejection is overcome in view of amended claim 12.

The Examiner asserted that the recitation "the disease" in claim 32 lacks proper antecedent basis. As recommended by the Examiner, claim 32 has been amended to recite "likelihood that the subject may develop or has developed cerebral vascular trauma or bleeding." Applicants submit that this rejection is overcome in view of amended claim 32.

The Examiner also asserted that the recitation "the presence of erythrocytes" in claim 33 lacks proper antecedent basis. As recommended by the Examiner, claim 33 has been amended to recite "the presence or past existence of erythrocytes in the sample or specimen." Applicants submit that this rejection is overcome in view of amended claim 33.

Further, the Examiner asserted that the recitations "9-BBN" and "The Grignard Reagent" in claim 35 are indefinite, asserting that it is not clear what the abbreviation "9-BBN" represents or what chemical is referred to by recitation of "The Grignard Reagent." Applicants respectfully disagree. Applicants submit that it is well known to one skilled in the chemical arts that the abbreviation 9-BBN represents 9-Borabicyclo[3.3.1]nonane, as demonstrated by Soderquist J., "A Simple, Remarkably Efficient Route to High Purity, Crystalline 9-B 9-Borabicyclo[3.3.1]nonane (9-BBN) Dimer," Org. Chem 1981, 46, 4599-4600 (a copy submitted herewith as Appendix A) and page 155 of the 2003-2004 Aldrich Handbook of Fine Chemicals and Laboratory Equipment (a copy submitted herewith as Appendix B). Claim 35 has been amended to recite "a grignard reagent." Applicants submit that grignard reagents are well known

to one of skill in the chemical arts, as demonstrated by page ONR-37 of the Twelfth Edition of the Merck Index, 1996 (a copy of which is submitted herewith as Appendix C) and the discussion of "Grignard reagent" in The Columbia Encyclopedia, Sixth Edition, 2001-05, accessed at www.bartleby.com/65/gr/Grignard-r.html on January 17, 2006 (a copy of which is submitted herewith as Appendix D).

Reconsideration and withdrawal of the rejection of claims 12, 32-33, and 35 under 35 U.S.C. §112, second paragraph, is respectfully requested.

The 35 U.S.C. §102(b) and §103(a) Rejections over Schwartz

The Examiner rejected claims 1, 6-7, 12, 14, 20-28, 31, and 34 under 35 U.S.C. §102(b) as being anticipated by Schwartz (U.S. Patent No. 4,378,971). Applicants note that claims 20 and 21 were cancelled in the Amendment and Response filed September 29, 2005, and request clarification for the inclusion of claims 20 and 21 in this rejection under 35 U.S.C. §102(b).

Additionally, the Examiner rejected claims 5, 9-11, 13, and 33 under 35 U.S.C. §103(a) as being unpatentable over Schwartz (U.S. Patent No. 4,378,971).

Applicants note that claim 8, which is not the subject of this rejection, recites "wherein the treated specimen fluoresces with a spectrum from about 530 to about 670 nm when excited at about 480 nm." Thus, while Applicants continue to traverse these rejections, claims 1, 9, 12, 14, 26, 31, 33, and 34 have been amended to recite, in accordance with claim 8, "wherein the . . . specimen fluoresces with a spectrum from about 530 nm to about 670 nm when excited at about 480 nm." Thus, as amended, claims 1, 5-7, 9-14, 22-28, 31, 33, and 34 are drawn to "wherein the . . . specimen fluoresces with a spectrum from about 530 nm to about 670 nm when excited at about 480 nm," thereby overcoming these rejections.

Reconsideration and withdrawal of the rejection of claims 1, 6-7, 12, 14, 22-28, 31, and 34 under 35 U.S.C. §102(b) as being anticipated by Schwartz (U.S. Patent No. 4,378,971) and the

The 35 U.S.C. §102(a) Rejection over Liu et al.

The Examiner rejected claims 9-11, 29-30, and 33 under 35 U.S.C. §102(a) as being anticipated by Liu et al. (abstract from *Society for Neuroscience Abstracts* submitted in the Information Disclosure Statement filed on September 29, 2005). Applicants respectfully submit that the rejection of claims 9-11, 29-30, and 33 under 35 U.S.C. § 102(a) as being anticipated by Liu et al. is overcome in view of the Declaration under CFR § 1.132 of Ke Jian Liu, filed herewith. Two of the authors of Liu et al., Ke Jian Liu and Shimin Liu, are inventors of the claimed invention. The remaining author of Liu et al., Stephen L. Peterson, is not an inventor of the subject matter of the claimed invention. Because Liu et al. was published within one year of the filing date of this application and the inventors of the claimed invention are also authors of the document, the document cannot properly be cited under 35 U.S.C. § 102(a). Withdrawal of the rejection of claims 9-11, 29-30, and 33 under 35 U.S.C. §102(a) as being anticipated by Liu et al. is respectfully requested.

The 35 U.S.C. §103 Rejection over Liu et al.

The Examiner rejected claims 1-8, 12-13, 26-28, 32, and 35 under 35 U.S.C. §103(a) as being unpatentable over Liu et al. (abstract from *Society for Neuroscience Abstracts* submitted in the Information Disclosure Statement filed on September 29, 2005). This rejection is respectfully traversed. As discussed in the section above, in view of the Declaration under CFR § 1.132 of Ke Jian Liu, filed herewith, Liu et al. does not qualify as prior art under 35 U.S.C. §102(a). Applicants respectfully submit that because Liu et al. does not qualify as prior art under 35 U.S.C. §102(a), it can not be used to substantiate a rejection under 35 U.S.C. §103. Reconsideration and withdrawal of the rejection of claims 1-8, 12-13, 26-28, 32, and 35 under 35 U.S.C. §103(a) as being unpatentable over Liu et al. is respectfully requested.

The 35 U.S.C. §103 Rejection over Liu et al. in view of Schwartz

The Examiner rejected claims 14-19, 22-25, 31, and 34 under 35 U.S.C. §103(a) as being unpatentable over Liu et al. in view of Schwartz. This rejection is respectfully traversed.

The 35 U.S.C. §103 Rejection over Liu et al. in view of Schwartz

The Examiner rejected claims 14-19, 22-25, 31, and 34 under 35 U.S.C. §103(a) as being unpatentable over Liu et al. in view of Schwartz. This rejection is respectfully traversed. In view of the Declaration under CFR § 1.132 of Ke Jian Liu, filed herewith, Liu et al. does not qualify as prior art under 35 U.S.C. §102(a). Applicants respectfully submit that because Liu et al. does not qualify as prior art under 35 U.S.C. §102(a), it can not be used to substantiate a rejection under 35 U.S.C. §103. Withdrawal of the rejection of claims 14-19, 22-25, 31, and 34 under 35 U.S.C. §103(a) as being unpatentable over Liu et al. in view of Schwartz is respectfully requested.

Finality of Office Action

Applicants respectfully submit that the finality of the Office Action mailed December 2, 2005, is improper. Applicants submit that claim 33 has been newly rejected under 35 U.S.C. §112, second paragraph (page 2 of Office Action mailed December 2, 2005), for the recitation "the presence of erythrocytes." Applicants respectfully note that the recitation "the presence of erythrocytes" is present in claim 33, as originally filed. Thus, this rejection of claim 33 is a new rejection not necessitated by Applicants' amendment of the claim and the finality of the Office Action mailed December 2, 2005, is improper (see M.P.E.P. § 706.07(a)). In the event that a Notice of Allowance is not issued in response to this Amendment and Response filed under 37 CFR §1.116, Applicants request that the finality of the Office Action mailed December 2, 2005 be officially withdrawn.

Summary

It is respectfully submitted that the pending claims 1-19 and 22-35 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted
By
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Feb 1, 2006
Date

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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 1st day of February 2006, at 2:45pm (Central Time).

By: Deb Schurmann
Name: Deb Schurmann

Appendix A

J. Org. Chem. 1981, 46, 4599-4600

Registry No. 1a, 621-22-7; 4, 78870-34-5; 5, 26243-62-9; 6, 78870-35-6; 7, 78870-36-7; 8, 78870-37-8.

A Simple, Remarkably Efficient Route to High Purity, Crystalline 9-Borabicyclo[3.3.1]nonane (9-BBN) Dimer

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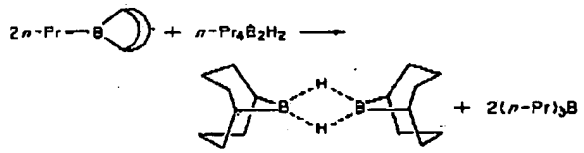
Received June 24, 1981

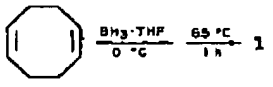
9-Borabicyclo[3.3.1]nonane (9-BBN) is a stable, crystalline dialkylborane, which, owing to its remarkable selectivity, has found wide application in organic synthesis.[1] We report a new, highly efficient preparation of crystalline 9-BBN dimer in high yield and purity from the cyclic hydroboration of 1,5-cyclooctadiene with borane–methyl sulfide complex, using 1,2-dimethoxyethane (monoglyme) as the reaction solvent. The product obtained under these conditions is resistant to decomposition in air and is indefinitely stable under a nitrogen atmosphere at room temperature. This development also makes possible the purification of 9-BBN from commercial and other sources to give a high purity, stable product.

First isolated and characterized by Köster,[2] 9-BBN dimer (1) was obtained from the thermal redistribution of *B*-*n*-propyl-9-BBN.



1

However, since the preparation of the *B*-alkyl-9-BBN derivative was itself a two-step process,[3] a more attractive route to 9-BBN was found by Knights and Brown, involving the cyclic hydroboration of 1,5-cyclooctadiene with borane–tetrahydrofuran complex.[4]



A 70:30 mixture of the isomeric 9-borabicyclo[3.3.1]- and [4.2.1]nonanes were formed in the initial cyclic hydroboration step. However, simply heating the mixture at reflux temperature effected equilibration of the boranes to give 1 exclusively. This procedure gives a microcrystalline product of mp 142 °C in ca. 65% yield. Further purification of this material by vacuum sublimation increases the melting point to 152–155 °C.[5]

While this approach is a particularly convenient method for the preparation of 9-BBN, it suffers from several practical difficulties which diminish the yield and purity of the crystalline product actually obtained. For one, the choice of BH_3-THF as the reagent used for the initial hydroboration necessarily requires that THF be used as the reaction solvent. However, 9-BBN is significantly soluble in this medium, presumably due, at least in part, to the presence of an equilibrium concentration (ca. 14%) (see Table I) of a 9-BBN·THF complex (2).

$$\underset{1}{(\text{9-BBN})_2} \overset{\text{THF}}{\rightleftharpoons} 2\,\underset{2}{\text{9-BBN-THF}}$$

Further, the microcrystalline product (1) obtained from THF solvent occasionally contains minor amounts of impurities which render the material pyrophoric.

Studies on the hydroboration of 1,5-cyclooctadiene using borane–methyl sulfide complex had revealed that this reagent could be used to prepare solutions of 9-BBN in solvents other than THF.[6] Of such solvents, the relatively low solubility of 9-BBN in diglyme[1] suggested that polyoxygenated ethers might provide an ideal reaction solvent to obtain the desired crystalline material.

The solubility of 9-BBN was measured in various solvents at 0 and 25 °C, and these results are summarized in Table II.

After investigating several solvent systems we found that monoglyme provided a superior reaction medium in that large crystals of 9-BBN dimer could be obtained in excellent yield (88%) and high purity (mp 153–155 °C). The high-purity crystalline 9-BBN dimer obtained from re-

Table I. Complexation of 9-BBN with Basic Solvents

base	% complex	^{11}B chemical shift[a] ($J_{^{11}B-H}$)
THF	14	13.9 (~90 Hz)
$S(CH_3)_2$	46	3.9 (107 Hz)
NC_5H_5[b]	100	−0.7 (88 Hz)

[a] Chemical shifts are reported in parts per million with BF_3-$O(CH_2CH_3)_2$ (δ = 0.00 ppm) as an external standard. Absorbances due to dimeric 9-BBN were observed at 28 ppm for the first two entries. The percent complexation was calculated from the relative peak areas from complexed vs. dimeric 9-BBN. [b] $CDCl_3$ was used as solvent in this case. Excess pyridine showed no measurable effect on the chemical shift of the boron resonance.

Table II. Molar Solubility of Dimeric 9-BBN in Representative Solvents[a]

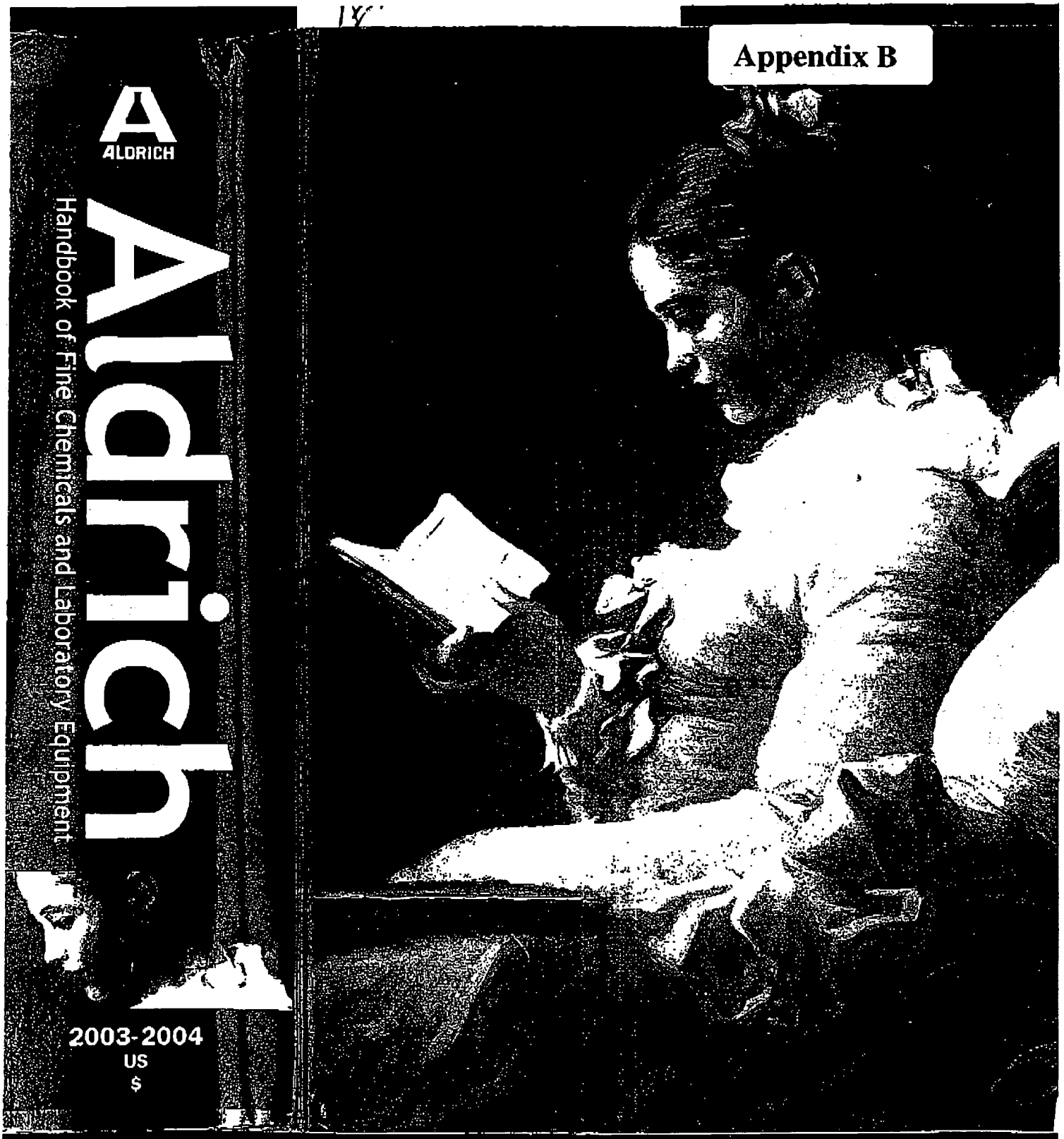
solvent	temperature 0 °C	temperature 25 °C
monoglyme	0.01	0.07
diglyme	<0.01	0.04
1,4-dioxane	0.03[b]	0.07
1,3-dioxolane	<0.01	0.04[c]
diethyl ether	0.09	0.18
tetrahydrofuran	0.12	0.29
dichloromethane	0.11	0.28
chloroform	0.21	0.50
carbon tetrachloride	0.15	0.36
pentane	0.13	0.23
hexane	0.11	0.25
benzene	0.19[d]	0.36
cyclohexane	0.03[e]	0.08
toluene	0.14	0.33
dimethyl sulfide		0.60[f]

[a] Values determined by hydride analysis.[1a] [b] 15 °C. [c] Some chemical change in 9-BBN was observed in this solvent. [d] 4.4 °C. [e] 7 °C. [f] Value taken from ref 1.

(1) Brown, H. C.; Lane, C. F. *Heterocycles* 1977, *7*, 453.
(2) Köster, R. *Angew. Chem.* 1960, *72*, 626.
(3) Köster, R.; Griassnov, G. *Angew. Chem.* 1961, *73*, 171.
(4) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* 1968, *90*, 5281.
(5) Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* 1974, *96*, 7765.
(6) Brown, H. C.; Mandal, A. K.; Kulkarni, S. U. *J. Org. Chem.* 1977, *42*, 1392.

0022-3263/81/1946-4599$01.25/0

Appendix B



A Young Girl Reading

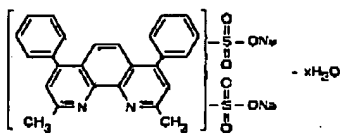
Appearing on our cover, *A Young Girl Reading* (oil on canvas, 81.1 cm x 64.8 cm) was painted ca. 1776 by the French painter Jean-Honoré Fragonard. A young woman is seen in profile, absorbed in her reading. The lavender ribbons in her hair, the lilac highlight of the plump magenta pillow against which she leans, and the creamy yellow of her dress were all executed with the spontaneous and energetic brushwork for which Fragonard is well known. As a young man, Fragonard studied with several artists whose rococo manner, with its fluid technique and pastel coloring, formed the basis of his own style. During the course of his long career, he painted historical, mythological, and allegorical compositions, fanciful "fêtes galantes" peopled by elegantly-dressed figures enjoying themselves in the open air, erotic canvases, and small genre paintings depicting intimate scenes of family life.

It is not known who is represented in this picture. We can see it, however, as the embodiment of several cultural developments which occurred during the course of the eighteenth century. The Industrial revolution and the expansion of wealth to a broader segment of the population, the spread of literacy and the growth of an educated middle class, and the development of the novel as a popular literary form all might be said to be manifest in this simple picture of a young girl reading a book. Changes in political and social consciousness, which ultimately contributed to the outbreak of the French revolution near the end of the century, also might be said to be expressed in this picture. The imaginary and often frivolous character of the fanciful decorative pictures Fragonard painted for aristocratic patrons has given way to realistic representation and sober concentration, although the luscious paint, the delicate touch and the shimmering color of Fragonard's rococo style are still present in this more straightforward subject.

This painting is a gift of Mrs. Ailsa Mellon Bruce to the National Gallery of Art in Washington, D.C., in memory of her father, Andrew W. Mellon.

If you would like a reproduction of this painting, we will be happy to send you a full-color print (11 in. x 14 in.) for $4.00 (to cover postage and handling). Please request **Z51,434-9** and specify ***A Young Girl Reading*** from the cover of the 2003–2004 Aldrich catalog. You can also contact us for a list of paintings that have appeared in Aldrich publications and are available as full-color prints.

			US $
	Bathocuproine, see 14,091-0, 2,9-Dimethyl-4,7-diphenyl-1,10-phenanthroline page 731		
14,662-5 ★	**Bathocuproinedisulfonic acid, disodium salt hydrate** [*52698-84-7*] (2,9-dimethyl-4,7-diphenyl-1,10-phenanthrolinedisulfonic acid, disodium salt) FW 564.55 mp 300° *FT-IR* 1(2),892C *R&S* 1(2),2657B Reagent used for determination of Cu^1 and Cu-protein complexes.[2] (1) *J. Electroanal. Chem.* 1993, *356*, 43. (2) *Clin. Chim. Acta* 1993, *216*, 103.	100mg 1g	11.00 58.30
	Bathophenanthroline, see 13,315-9, 4,7-Diphenyl-1,10-phenanthroline page 780		
14,661-7 ★	**Bathophenanthrolinedisulfonic acid, disodium salt hydrate** [*52746-49-3*] (4,7-diphenyl-1,10-phenanthrolinedisulfonicacid, disodium salt) FW 536.50 mp 300° *FT-NMR* 1(3),479B *FT-IR* 1(2),892B *R&S* 1(2),2657A *UV-Vis* 133	100mg 1g 5g	13.60 73.60 291.90
B40-2	**DL-Batyl alcohol,** 95% [*544-62-7*] (DL-3-octadecyloxy-1,2-propanediol) $CH_3(CH_2)_{17}OCH_2CH(OH)CH_2OH$ FW 344.58 mp 71-73° *Merck Index* 13,1014 *FT-NMR* 1(1),342A *FT-IR* 1(1),228A *Safety* 2,339D *R&S* 1(1),225F *RTECS#* TZ0960000 *IRRITANT*	1g 10g	17.40 97.70
	BBD, see B 1889, 7-Benzylamino-4-nitrobenz-2-oxa-1,3-diazole page 178		
17,671-3	**9-BBN dimer,** crystalline, 98% [*21205-91-4*] (9-borabicyclo[3.3.1]nonane) FW 244.04 mp 150-152° *Fiesor* 2,31 3,24 4,41 5,46 6,62 7,29 8,47 10,48 15,43 17,49 *FT-IR* 1(2),1131D *Safety* 2,340B *R&S* 1(2),3019H *FLAMMABLE SOLID MOISTURE-SENSITIVE* Employed in the hydroboration of alkynes,[1] nitriles,[2] and ketones.[3] (1) *Tetrahedron Lett.* 1991, *32*, 6239. (2) *Chem. Ber.* 1993, *126*, 285. (3) *Synlett* 1991, 349. *(25g and 100g units packaged under nitrogen in Sure/Seal™ bottles)*	5g 25g 100g	56.50 168.70 470.50
15,107-6	**9-BBN,** 0.5*M* solution in tetrahydrofuran [*280-64-8*] (9-borabicyclo[3.3.1]nonane) FW 122.02 d 0.894 Fp 1°F(-17°C) *Fiesor* 2,31 3,24 4,41 5,46 6,62 7,29 8,47 9,57 10,48 11,68 14,52 15,43 *Safety* 2,340D *FLAMMABLE LIQUID MOISTURE-SENSITIVE* *(Packaged under nitrogen. 100 and 800mL in Sure/Seal™ bottles, 8 and 18L in Kilo-Lab™ metal cylinders. Cylinder-outlet valve or transfer line needed to dispense material. Cylinders require deposit.)*	100mL 800mL 8L 18L	28.50 113.60 500.20 981.20
45,949-6	**9-BBN,** 0.4*M* solution in hexanes [*280-64-8*] (9-borabicyclo[3.3.1]nonane) FW 122.02 bp 68-70° d 0.691 Fp -15°F(-26°C) *FLAMMABLE LIQUID*	100mL 1L	70.00 384.80
	9-BBN-nopol benzyl ether adduct, 0.5*M* solution in tetrahydrofuran, see 27,010-5, NB-Enantrane™ page 1325		
25,313-8	**9-BBN triflate,** 0.5*M* solution in hexanes [*62731-43-5*] (9-borabicyclo[3.3.1]nonyl trifluoromethanesulfonate) FW 270.08 d 0.733 Fp -9°F(-22°C) *Safety* 2,341B *FLAMMABLE LIQUID MOISTURE-SENSITIVE* *(Packaged under nitrogen in Sure/Seal™ bottles)*	100mL 800mL	109.00 492.40
	BBOD, see 41,653-3, 2,5-Bis(4-biphenylyl)-1,3,4-oxadiazole page 209		
	BBOT, see 2,5-Bis(5-*tert*-butyl-2-benzoxazolyl)thiophene		
	BCG, see Bromocresol Green		
	BCH, see 22,552-5, 2-Amino-2-norbornanecarboxylic acid page 101		
	BCP, see Bromocresol Purple		
	BCPB, see 21,298-9, Bromochlorophenol Blue, water soluble page 277		
21,476-0	**BDCS Silylation Reagent** d 0.959 Fp 136°F(57°C) *Safety* 2,341C *R&S* 1(2),3007M .. *CANCER SUSPECT AGENT CORROSIVE* *(5mL in ampule. 100mL units packaged under nitrogen in Sure/Seal™ bottles)*	5mL 6x5mL 100mL	15.70 61.90 37.10
	BDMA, see *N,N*-Dimethylbenzylamine		



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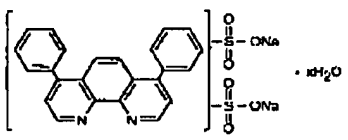
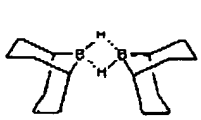


14,661-7



17,671-3

45,949-6

Appendix C

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

TWELFTH EDITION

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Maryadele J. O'Neil, *Senior Associate Editor*
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Published by
Merck Research Laboratories
Division of
MERCK & CO., INC.
Whitehouse Station, NJ

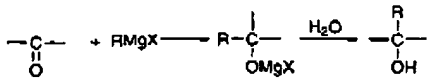
1996

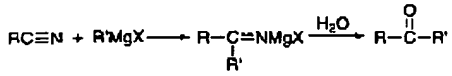
V. Grignard, *Compt. Rend.* **130**, 1322 (1900); F. F. Blicke, *Heterocyclic Compounds* **1**, 222 (1950); K. Nützel, *Houben-Weyl* **13/2a**, 128 (1973).

155. Grignard Reaction

V. Grignard, *Compt. Rend.* **130**, 1322 (1900).

Traditionally, it is the addition of organomagnesium compounds (Grignard reagents) to carbonyl compounds to generate alcohols. A more modern interpretation extends the scope of the reaction to include the addition of Grignard reagents to a wide variety of electrophilic substrates:



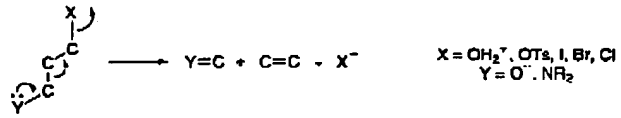


Early review: D. A. Shirley, *Org. React.* **8**, 28-58 (1954). Preparation of Grignard reagents: Y. H. Lai, *Synthesis* **1981**, 585-604. Mechanistic study: K. Maruyama, T. Katagiri, *J. Phys. Org. Chem.* **2**, 205 (1989). Review of stereoselective addition of carbonyl compounds: D. M. Huryn, *Comp. Org. Syn.* **1**, 49-75 (1991). General review: G. S. Silverman, P. E. Rakita in Kirk-Othmer *Encyclopedia of Chemical Technology* vol. 12 (Wiley-Interscience, New York, 4th ed., 1994) pp 768-786. *Cf.* Barbier(-type) Reaction.

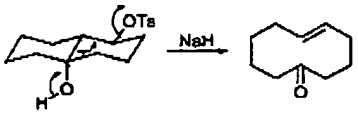
156. Grob Fragmentation

C. A. Grob, W. Baumann, *Helv. Chim. Acta* **38**, 594 (1955).

Carbon-carbon bond cleavage primarily *via* a concerted process involving a five atom system:



The intramolecular version is useful for the preparation of medium-size rings:

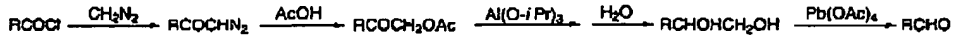


C. A. Grob, *Angew. Chem. Int. Ed.* **8**, 535-546 (1969); L. Birladeanu *et al.*, *J. Am. Chem. Soc.* **92**, 6387 (1970); S. Schreiber, *ibid.* **102**, 6163 (1980); J. R. Mahajan, H. C. deAraújo, *Synthesis* **1981**, 49; M. Ochiai *et al.*, *J. Org. Chem.* **54**, 4832 (1989); X. L. Armesto *et al.*, *ibid.* **59**, 4659 (1994); P. Weyerstahl, H. Marschall, *Comp. Org. Syn.* **6**, 1044-1065 (1991). *Cf.* Eschenmoser Fragmentation; Wharton Reaction.

157. Grundmann Aldehyde Synthesis

C. Grundmann, *Ann.* **524**, 31 (1936).

Transformation of an acid into an aldehyde of the same chain length by conversion of the acid chloride, *via* the diazo ketone, to the acetoxy ketone, reduction with aluminum isopropoxide and hydrolysis to the glycol, and cleavage with lead tetraacetate:



E. Moseting, *Org. React.* **8**, 225 (1954); O. Bayer, *Houben-Weyl* **7/1**, 239 (1954); H. K. Mangold, *J. Org. Chem.* **24**, 405 (1959). *Cf.* Sonn-Müller Method; Stephen Aldehyde Synthesis.

158. Guareschi-Thorpe Condensation

I. Guareschi, *Mem. Reale Accad. Sci. Torino* **II**, 46, 7, 11, 25 (1896); H. Baron, F. G. P. Renfry, J. F. Thorpe, *J. Chem. Soc.* **85**, 1726 (1904).

Grignard reagent. The Columbia Encyclopedia, Sixth Edition. 2001-05

Appendix D

The Columbia Encyclopedia, Sixth Edition. 2001-05.

Grignard reagent

(grēnyärd´ rēā´jənt) (KEY), any of an important class of extremely reactive chemical compounds used in the synthesis of hydrocarbons, alcohols, carboxylic acids, and other compounds. Chemically, a Grignard reagent is an organic magnesium halide dissolved in a nonreactive solvent (typically dry ethyl ether). The substance is made up of an organic group, e.g., an alkyl or aryl group, joined by a highly polar covalent bond (see chemical bond) to magnesium, while the magnesium is joined by an ionic bond to a halogen ion, e.g., bromide or iodide. A Grignard reagent will react with water, oxygen, carbon dioxide, or almost any electrophilic organic compound. The reaction of Grignard reagents with aldehydes to form alcohols is of particular importance in the laboratory. Because Grignard reagents are so unstable, they are generally prepared just before use by reacting an organic halide, e.g., methyl iodide, with magnesium metal in a completely dry solvent; air is usually excluded from the reaction vessel, e.g., by flushing it with nitrogen. Grignard reagents are named after Victor Grignard, a French chemist, who received a Nobel Prize (1912) for their discovery.

PATENT
Docket No. 310.00370101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Liu et al.	Group Art Unit:	1743
Serial No.:	10/673,538	Examiner:	Maureen Wallenhorst
Confirmation No.:	1846		
Filed:	September 29, 2003		
For:	METHODS AND KITS FOR THE DETECTION OF ERYTHROCYTES		

DECLARATION UNDER 37 C.F.R. § 132

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Ke Jian Liu, declare and say as follows:

1. I am a co-inventor of the subject matter claimed in the above-identified U.S. Patent Application Serial No. 10/673,538, filed September 29, 2003.

2. I received a Ph.D. in Radiation Biochemistry from the University of Leeds, England, in 1988 and a B.Sc. in Chemistry from Beijing University, China, in 1982. I have been employed since 1999 at the College of Pharmacy, University of New Mexico (UNM), Albuquerque, New Mexico. Since 2002 I have been an Associate Professor of Medicinal Chemistry and Toxicology, College of Pharmacy, UNM; since 2003 I have been an Associate Professor of Neurology, School of Medicine, UNM; since 2000 I have been the Director of the Electron Paramagnetic Resonance (EPR) Core Facility, University of New Mexico Health Science Center; and from 1999-2002 I was an Assistant Professor, College of Pharmacy, UNM. From 1993-1999 I was employed by the Department of Radiology, Dartmouth Medical School, Hanover, New Hampshire as a Research Assistant Professor; from 1990-1993 I was employed by the Department of Biophysics and Physiology, University of Illinois at Urbana-Champaign, Illinois, as a Research Specialist in Bio-organic Chemistry; and from 1988-1989 I was a Postdoctoral Research Associate with the Radiation Laboratory, University of Notre Dame, Indiana. My research activities include the study of the toxicity and carcinogenicity of metal ions

and the study of cerebral injury due to stroke, with a central focus on the role of free radicals in signal transduction, and its associated oxidative damage. I have over 100 peer-reviewed publications on these and related topics.

3. I am familiar with Liu et al., "Visualization of the early 'no-reflow phenomenon' in rats subjected to focal cerebral ischemia and reperfusion," Society for Neuroscience Abstracts 2001;27(1):1157 (Abstract #434.16) (hereinafter "Liu et al.") and make this Declaration in support of the patentability of the claims of application Serial No. 10/673,538.

4. I am a co-author of the Liu et al. document referenced in paragraph 3. The other authors of Liu et al. are Shimin Liu and Stephen L. Peterson.

5. Shimin Liu, M.D., Ph.D., is a co-inventor of the subject matter claimed in the above-identified U.S. patent application Serial No. 10/673, 538. Dr. Shimin Liu was employed at the College of Pharmacy, University of New Mexico, Albuquerque, New Mexico, as a Research Assistant Professor from 2004 to 2005, and as a Research Scientist from 2002 to 2003, and worked in my laboratory during that time.

6. Stephen L. Peterson, Ph.D., Professor of Toxicology, College of Pharmacy, University of New Mexico, Albuquerque, New Mexico, provided general technical assistance and laboratory equipment used by Dr. Shimin Liu and myself during the development of the subject matter referenced in Liu et al. Dr. Peterson was included as a co-author of Liu et al., however, he is not a co-inventor of the subject matter claimed in U.S. patent application Serial No. 10/673,538, and, to the extent he was involved, he worked under my direction and supervision.

7. I further declare that statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 1/26/06 By: Ke-G
Ke Jian Liu